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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WANG, CHANG YU	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 11/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/812,144	BRIEND ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Sep 18, 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-101* is/are pending in the application.

4a) Of the above claim(s) *9, 10, 12-14, 23, 26, 29, 32, 35, 37, 40, 48, 52, 58, 59, 66,69-96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/24/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims rejected are 1-8,11,15-22,24,25,27,28,30,31,33,34,36,38,39,41-47,49-51,53-57,60-65,67,68 and 97-101.

DETAILED ACTION

Status of Application/ Election/Restrictions

Applicant's election with traverse of Group I (claims 1-69), compounds, in vivo, down-regulate/inhibitor, regulatory T cells, small molecule, IL-10 in the reply filed on September 18, 2006 is acknowledged. The traversal is on the ground(s) that searching Groups I, III, V and VI is not an undue burden for the examiner because the search of Groups I, III, V and VI is coextensive and Groups I and VI are classified in the same class. This is not found persuasive because an application may properly be required to be restricted to one of two or more claimed inventions if they are able to support separate patents and they are either independent (MPEP § 806.04 - § 806.04 (j)) or distinct (MPEP § 806.05 - § 806.05 (i)). The Examiner has shown that the Groups I, III, V and VI are independent or distinct for the reasons in the previous Office action (see Paper mailed on June 16, 2004). Furthermore, MPEP § 803 provides that the separate classification (i.e., class and subclass) of distinct inventions is sufficient to establish a *prima facie* case that the search and examination of the plural inventions would impose a serious burden upon the Examiner; such separate classification was set forth in the previous Office action. Groups I, III, V and VI encompass divergent subject matter. The outcomes/steps/effects of a method of modulating an immune response (Group I) are different from those in a method of screening a modulator (Group VI), vaccination (Group V) in a subject with tumors or a method of preparing lymphocytes (Group III). Since the subject matter of Groups I, III, V and VI is divergent, it would require different

searches and analyses. There can be a search burden even if the classification is the same. The search for Group I is not the same as the search for a method for producing of lymphocytes (Group III), a method of vaccination (Group V) or a method of screening for a modulator (Group VI), indicating that the searches are not coextensive and can provide a search burden to the examiner. However, upon reconsideration, the requirement of species election on T cells and cytokines is withdrawn. The subject matter to the extent of effector, helper, and cytotoxic T cells and cytokines will be included in this examination.

The requirement for the rest of restriction is still deemed proper and is therefore made FINAL.

Claims 1-96 and newly added claims 97-101 are pending. Claims 70-96 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. In addition, claims 9, 10, 12-14, 23, 26, 29, 32, 35, 37, 40, 48, 52, 58, 59, 66 and 69 are also withdrawn from further consideration because of non-elected species. Claims 1-8, 11, 15-22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 38, 39, 41-47, 49-51, 53-57, 60-65, 67, 68 and new claims 97-101 are under examination in this office action.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Objections

Claims 4, 8 are objected to as encompassing non-elected species.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 11, 15-22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 38, 39, 41-47, 49-51, 53-57, 60-65, 67, 68 and 97-101 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting the Notch signaling induced by Delta-1 (a Notch ligand) in C2C12 cells and Jurkat-N2 cells with MW167 detected by measuring the activity of HESE-1 luciferase, and enabling for inhibiting the production of notch-mediated cytokines by measuring decreased IL-10 and increased IL-5 in human CD4+ T cells isolated from peripheral blood in vitro, does not reasonably provide enablement for a method for modulating any immune response comprising administering a modulator of Notch intracellular domain (Notch IC) protease activity in vivo and treating a T-cell mediated disease or infection as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

"There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'. These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)". See MPEP § 2164.01.

Claims 1-8, 11, 15-22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 41-47, 49, 51, 53-57, 60-65, 97-101 are directed to a method for modulating an immune response comprising administering an inhibitor of Notch intracellular domain (Notch IC) protease activity in vivo wherein the inhibitor is a small molecule compound and down-regulates the Notch signaling pathway. Claims 38, 39, 67, 68 are directed to a method for modulating an immune response to treat a T-cell mediated disease or infection comprising administering an inhibitor of Notch intracellular domain (Notch IC) protease activity in

vivo wherein the inhibitor is a small molecule compound and down-regulates the Notch signaling pathway. Applicant describes that MW167 (a γ-secretase inhibitor II purchased from Calbiochem) inhibits the Notch signaling in C2C12 cells transfected with an mHES1-luciferase reporter construct by detecting the luciferase activity using an ELISA method. Applicant describes that the production of increased IL-10 and decreased IL-5 induced by Delta in human $CD4^+$ T cells can be reversed by MW167. Applicant also describes that the Notch signaling can be inhibited by MW167 in Jurkat-N2 cells.

Based on the specification, Applicant is enabled for inhibiting the Notch signaling in heterologous cells transfected with a reporter gene of Notch by MW167 in vitro. In addition, Applicant is enabled for inhibiting the production of IL-10 and enhancing the production of IL-5 in human $CD4^+$ T cells by MW167. However, the instant specification fails to provide sufficient guidance as to enable one of skill in the art to practice the full scope of the claimed invention. Applicant fails to teach what other proteases other than presenilin or γ-secretase are as recited in claim 1 since the art only recognizes that presenilin and γ-secretase are able to release the intracellular domain of Notch. Applicant fails to teach what a specific immune response would be changed and to be evaluated in a condition of administration of any inhibitor of Notch IC protease activity as recited in claim 1 since the responses of the immune system respond to different antigens or diseases are different. Although Notch has been shown to be involved in thymocyte development and activation of Notch signaling has been shown to reduce T cell activation in allergy and graft rejection, it is impossible to predict the relationship between the inhibitor and the immune response since the immune response and

antigen are unknown. Applicant also fails to teach what specific cytokines could be generated under any specific immune response as recited in claim 42. Thus, an ordinary skill in the art cannot contemplate what specific effects to be evaluated and determine whether the inhibitor of the Notch IC protease activity could inhibit or enhance any specific cellular/humoral immune response.

It is known in the art that activation of the Notch signaling pathway is mediated through the binding of a Notch ligand, such as Delta/Serrate-1, to activate the cleavage of the extracellular domain of Notch by a TACE (TNF-α convertase enzyme) or AMD (metalloprotease) and the cleavage of intramembrane domain by presenilin or presenilin-dependent γ-secretase like protease to release the intracellular domain of Notch to activate the downsteam signaling pathways (see p. 382, abstract, Schroeter et al. Nature. 1998. 393: 382-386). It is also known in the art that activation of the Notch signaling pathway by Delta/Serrate-1 can reduce activation of T-cells that are involved in allergy and graft rejection (see col. 13-16, Examples 9-12; col. 83-84, claims 1-6 US Patent No. 6887475). Activation of the Notch signaling pathway by Serrate-1/Delta induces regulatory T cells for immune tolerance and reduced production of IL-2 (see col. 11, lines 22-41). In addition, inhibiting the activity of presenilin by antisense oligonucleotides of presenilin has been shown to inhibit tumor growth because under the condition of p53-mediated apoptosis, the expression of presenilin is repressed (see col. 18, Example 2; col.21-24, claims 1-16, US Patent No. 6635483, issued Oct 21, 2003).

The Notch signaling has been shown to be involved in peripheral immune responses by upregulating regulatory $CD4^+$ T cells for immune tolerance (p. 215, abstract. Hoyne et al. Immunol. Rev. 2001. 182: 215-227). In addition, Notch has also been shown to be involved in maturation of $CD4^+$ or $CD8^+$ T cells (Hadland et al. PNAS, 2001. June 19. 98: 7487-7491). Hadland et al. teach that Notch signaling is involved in maturation of $CD4^+CD8^+$ double positive thymocytes into $CD4^+$ or $CD8^+$ single positive T cells. Thus, it is predictable that an inhibitor inhibiting the Notch signaling pathway would decrease regulatory $CD4^+$ T cells and decrease IL-10 since activation of the Notch signaling pathway increases regulatory $CD4^+$ T cells and regulatory $CD4^+$ T cells secrete IL-10. It is also predictable that inhibiting the Notch signaling would also inhibit the maturation of $CD4^+$ or $CD8^+$ cells. However, it is unpredictable how an inhibitor inhibiting the Notch signaling pathway would inhibit or enhance any immune response in vivo as in claims 1 and 97, increase specific subsets of T cytotoxicity cells as in claims 24, 25 or regulate the production of other cytokines as in claims 42-47, 49, 51, 53-57, 60-68 since Applicant fails to limit/specify a specific immune response. Thus, a skill artisan cannot contemplate an immune response in the presence of the inhibitor of the Notch IC protease activity. It has been shown that lowering the level of Notch IC by γ-secretase inhibitors inhibits the development of $CD8^+$ SP cells (see p. 7487, abstract. Hadland et al. PNAS, 2001. June 19. 98: 7487-7491). Lowering Notch1 activity after T cell receptor-directed lineage commitment represses the maturation of $CD8^+$ SP thymocytes but not $CD4^+$ SP cells. Thus, it is unpredictable whether an inhibitor of the Notch IC protease activity would increase cytotoxicity $CD8^+$ cells. Applicant is enabled

for enhancing/inhibiting activation of regulatory $CD4^+$ T cells since it has been shown that activation of the Notch signaling pathway by Notch ligands can reduce T cell activation in a condition of immune tolerance, such as allergy and graft rejection. However, Applicant fails to teach what other responses could be affected by regulating the Notch signaling pathway since it is still not clear the molecular mechanisms of the Notch signaling underlying an immune response against to an characterized antigen.

The immune response is an orchestrated activity between the cellular immunity (Th1 immune response) and the humoral immunity (Th2 immune response). The general accepted hypothesis is that recognition of an antigen by $CD4^+$ T cells can result in either productive immunity or the induction of tolerance. $CD4^+$ T cells include Th1 cells, Th2 cells and Tr cells. Regulatory T cells include $CD4^+CD25^+$ T regulatory cells, IL-1 secreting Tr1 cells and Th3 cells. T cell activation in the presence of IL-12 can induce the formation of Th1 cells that promote cell-mediated immune responses to an antigen. IL-4 can direct $CD4^+$ T cells to differentiate to Th2 cells that are effective in promoting humoral immunity. IL-10 can promote the differentiation of $CD4^+$ T cells into regulatory T (Tr) cells to suppress immune response. Th1 cells secrete IL-2, IFN-γ, TNF-α and lymphotoxin-β. Th2 cells secrete IL-4, IL-5, IL-9 and IL-13. Tr cells secrete inhibitory cytokines such as IL-10 and TGF-β1 (see p. 219. Hoyne et al. Immunol. Rev. 2001. 182: 215-227, as in IDS). However, different diseases have different responses and different corresponding subsets of cytokines and cells that are associated with the diseases. The cell populations responsible for the activation of the cellular and humoral immune responses in tumor/infection are different from those in allergy, graft rejection

or autoimmunity. For example, increased activation of $CD8^+$ cytotoxicity T cells and natural killer cells are responsible for an immune response against tumor cells whereas the activity of $CD8^+$ T cells is decreased to help the growth of a graft. In addition, since Applicant fails to limit a specific immune response and also fails to limit a "selected antigen or antigen determinant", "a tumor antigen" or "an antigen of a pathogen" as in claims 15-17, it would be impossible to predict what specific lymphocyte activity is as in claim 18 and T-cell activity is as in claim 19. Although the art recognizes that activation of the Notch signaling pathway can reduce T cell activation in allergy and graft rejection, Applicant fails to teach how an inhibitor of the Notch IC protease activity would affect other immune responses as in claim 1 other than activation of regulatory $CD4^+$ T cells in immune tolerance since both cellular immunity and humroal immunity are responsible for an infection or tumor and are also responsible for immune tolerance or autoimmunity.

In addition, claims 38, 39, 67, 68 are directed to a method for modulating an immune response to treat a T-cell mediated disease or infection comprising administering an inhibitor of Notch intracellular domain (Notch IC) protease activity in vivo wherein the inhibitor is a small molecule compound and down-regulates the Notch signaling pathway. The specification fails to provide sufficient guidance as to how to use any of the claimed inhibitors to treat any T-cell mediated disease. Applicant has provided no working example that any inhibitors down-regulating the Notch signaling pathway could be used for treating any T-cell mediated disease, allergy, graft rejection, tumor or infection as recited in the claims and it is unknown how inhibition of the Notch

signaling pathway is related to any T-cell mediated disease. In addition, activation of the Notch signaling by Notch ligands can reduce T cell activation in allergy and graft rejection (see col. US Patent No. 6887475). An inhibitor of the Notch signaling pathway would predictably reverse the reduced T cell activation involved in allergy and graft rejection, which is a condition with the opposite T cell activity. However, Applicant fails to provide sufficient guidance as to how the reversed condition of reduced T cell activation (ie. enhanced T cell activation) plays a role in an immune response and is related to the treatment of allergy, autoimmunity, graft rejection as in claims 39 and 68. The reduced activation of T cells by an activator of the Notch signaling pathway in allergy, autoimmunity or graft rejection is a beneficial effect of immune tolerance to help growth of graft or tolerate allergens. However, it is unpredictable whether reduced T cell activation reversed by an inhibitor of the Notch IC protease activity would be a beneficial result to the immune system in a condition of allergy, autoimmunity or graft rejection as in claims 39 and 68, indicating that undue experimentation is required to practice the claimed invention. In addition, although Applicant describes that MW167 decreases the production of IL-10 and increases IL-5 in $CD4^+$ T cells, Applicant fails to provide any guidance as to how to apply the in vitro findings to treating the diseases as recited in the claims since $CD4^+$ T cells include Th1 cells, Th2 cells and Tr cells. IL-10 is secreted by regulatory $CD4^+$ T cells, which are responsible for immune tolerance or immunosuppression. IL-5 is secreted by Th2 cells, which are responsible for the humoral immunity. However, Applicant fails to establish a nexus between the production

of IL-10 or IL-5 and any diseases. Thus, it is unpredictable whether MW167 could be used in treating any T-cell mediated disease.

Furthermore, the claims are not limited to using MW167. Applicant fails to teach what other modulators/inhibitors could be used in the claimed method in modulating any immune response as recite in claim 1 or modulating the production of cytokines as in claim 42. The art recognizes that cyclohexamide, actinomycine D (known inhibitors for transcription/translation that can inhibit the expression/activity of presenilin or γ-secretase), antisense oligonucleotidies of presenilin, anti-presenilin, and anti-γ-secretase as in US 6635483, and γ-secretase inhibitors, such as MDL 28170, MG132 and MW167 are able to inhibit the protease activity of presenilin and γ-secretase, which inhibits the Notch IC protease activity to release Notch IC and the Notch signaling pathway (see p. 520, 1st col., 1st paragraph to 2nd col., 2nd paragraph, Strooper et al. Nature. 1999. 398: 518-522 as in IDS submitted 8/24/04). However, Applicant fails to teach whether the inhibitors as mentioned above could be used in modulating any immune response and how to modulate any immune response since there is no guidance on how to use these inhibitors in modulating any immune response against any antigen or immune activity. Therefore, in view of the necessity of experimentation, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to a method for modulating an immune response to treat a T-cell mediated disease or infection comprising administering an inhibitor of Notch intracellular domain (Notch IC) protease

activity in vivo wherein the inhibitor is a small molecule compound and down-regulates the Notch signaling pathway.

Claims 1-8, 11, 15-22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 38, 39, 41-47, 49-51, 53-57, 60-65, 67, 68 and 97-101 are further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Claims 1-8, 11, 15-22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 41-47, 49, 51, 53-57, 60-65, 97-101 are directed to a method for modulating an immune response comprising administering an inhibitor of Notch intracellular domain (Notch IC) protease activity in vivo wherein the inhibitor is a small molecule compound and down-regulates the Notch signaling pathway. Claims 38, 39, 67, 68 are directed to a method for modulating an immune response to treat a T-cell mediated disease or infection comprising administering an inhibitor of Notch intracellular domain (Notch IC) protease activity in vivo wherein the inhibitor is a small molecule compound and down-regulates the Notch

signaling pathway. Applicant recites "a modulator" in claims 1, 2, 5, 6, 11, 16, 36, 42, 65. Applicant recites "an inhibitor" in claims 22, 25, 28, 31, 34, 47, 51, 60, 61, 97, 98, 100, 101. Claims 3, 4, 7, 8, 15, 17-21, 24, 27, 30, 41, 43-46, 49, 53-57, 62-64, 99 are dependent claims. However, Applicant fails to teach what other common structures/characteristics are required for a modulator or an inhibitor to be used in the claimed invention other than modulating/down-regulating the Notch signaling pathway.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant has possession of and what Applicant is claiming. From the specification, it is clear that Applicant has possession of MW167, cyclohexamides, anti-presenilin, anti-γ-secretase or antisense oligonucleotides of presenilin as in US 6635483 or other known inhibitors for transcription/translation that can inhibit the expression/activity of presenilin or γ-secretase, such as cyclohexamine, actinomycine D. However, the clams are not limited to the molecules as mentioned above. Applicant is not in possession of any modulator or any inhibitor that inhibits the notch IC protease activity or inhibits the Notch signaling pathway as recite in the claims. Applicant fails to specify/describe what other modulators/inhibitors are and could be used in the claimed methods or in treating the claimed diseases as in claims 38, 39, 67 and 68. Applicant fails to teach what other common structures/characteristics are required for the modulators/inhibitors that are able to inhibit the Notch IC protease activity and inhibit the Notch signaling pathway. Since the other structure/characteristics of the

modulators/inhibitors are not known, a skilled artisan cannot contemplate what other modulators/inhibitors can be used in the claimed methods.

Adequate written description requires more than a mere statement that it is part of the invention. A description of a genus of polypeptides/ compounds may be achieved by means of a recitation of a representative number of polypeptide sequences/chemical groups, defined by amino acid sequence/chemical structure, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Therefore, a method for modulating an immune response comprising administering an inhibitor of Notch intracellular domain (Notch IC) protease activity in vivo wherein the inhibitor is a small molecule compound and down-regulates the Notch signaling pathway and a method for modulating an immune response to treat a T-cell mediated disease or infection comprising administering an inhibitor of Notch intracellular

domain (Notch IC) protease activity in vivo wherein the inhibitor is a small molecule compound and down-regulates the Notch signaling pathway have not met the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 11, 15-22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 38, 39, 41-47, 49-51, 53-57, 60-65, 67, 68 and 97-101 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: Applicant fails to point out the subject to be administered in the method of modulating an immune response, which renders the step of administration incomplete.

Claims 1-8, 11, 15-22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 38, 39, 41-47, 49-51, 53-57, 60-65, 67, 68 and 97-101 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8, 11, 15-22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 38, 39, 41-47, 49-51, 53-57, 60-65, 67, 68 and 97-101 are indefinite because Applicant recites "modulating/modulators" in claims 1, 5, 6, 11,18, 19, 22, 25, 42, 97 and "modified" in claims 62 and 63. Claims 3, 4, 15-22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 38, 39, 41 depend from claim 1. Claims 43-47, 49-51, 53-57, 60-65, 67, 68 depend from claim 42. Claims 98-101 depend from claim 97. However, Applicant fails to limit the word "modulating/modulator/modified" as recited in the claims. A compound can either enhance or inhibit a function and subsequently alleviate or potentially treat a disorder associated with the function. Since Applicant has not limited the immune response and T-cell mediated disease or infection, it is unclear how an agent that can either enhance or inhibit the activity of the Notch IC protease activity is related to any immune response or any T-cell mediated disease. It is also unpredictable whether an agent enhancing or inhibiting the activity of Notch intracellular domain (Notch IC) protease activity could be used to potentially inhibit/enhance an immune response in treating a disease. Thus, the claims are indefinite.

Claims 2-4, 6-8, 11 are indefinite because Applicant recites "agonist" in the claims 2 and 6. Claims 3-4, 7-8 and 11 depend from claims 2 and 6. The claims are drawn to a method of modulating an immune response comprising administering a modulator of Notch IC protease activity that down regulates the Notch signaling pathway. An agonist of presenilin or presenilin-dependent gamma-secretase would activate and enhance the activity of presenilin. It is known in the art that the cascade of the activation of Notch signaling by Notch ligands, such as delta, is through the

cleavage of the extracellular domain of Notch by an extracellular convertase such as TACE or metalloproteases (ADAMs) and a cleavage of intracellular domain of Notch by presenilin or presenilin-dependent γ-secretase like protease (Strooper et al. Nature. 1999. 398: 518-5522 as in IDS). Thus, an agonist regularly activates and increases the activity of a receptor (in this case, it's presenilin) and subsequently enhances a downstream signaling pathway (in this case, it's the Notch signaling pathway) whereas an antagonist regularly inhibits the activation and decreases the function of a receptor. The language of the claim is not clear, thus the claims are indefinite.

Claims 5-8 and 11 are indefinite because Applicant recites "Notch signaling pathway" in claims 5 and 11. Claims 6-8 depend from claim 5. However, Applicant fails to limit what the specific Notch signaling pathway is and how it is related to any immune response. Although Applicant provides few examples of the Notch signaling pathway on p. 25 of the specification, Applicant fails to define/specify what is/is not included within the limitations of the claims. The disclosure also fails to set for the metes and bounds of what is encompassed within the definition of "the Notch signaling pathway". Thus the artisan would not know what responses Applicant intended to measure.

Claim 101 is indefinite because the term "MW167" recited in the claim without a reference to its precise structure or providing a full name for abbreviated names. Without identification of property or combination of properties, which are unique to and, therefore, definitive of the instant recitations, the metes and bounds of the claims remain undetermined. Further, the use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use

the same laboratory designations to define completely distinct molecules. The rejection can be obviated by amending the claims to specifically and uniquely identify MW167, for example, by a precise structure and a specific function of MW167.

Obviousness-Type Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8, 11, 15-22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 38, 39, 41-47, 49-51, 53-57, 60-65, 67, 68 and 97-101 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 8, 10, 12, 14-16 of copending Application No. 10/765727 ('727), claims 16-32, 61-70, 72 of copending Application No. 10/846989 ('989), claims 28-61, 86, 100-119 of copending Application No. 10/845834 ('834), claims 1-16 of copending Application No.10/899422

('422), claims 24-33 of copending Application No. 10/958784 ('784), claims 17-20 of copending Application No.11/058066 ('066), claims 1-20 of copending Application No. 11/178724 ('724), claims 1-7 of copending Application No.11/071796 ('796), claims 65, 68-73 of copending Application No. 11/232404 ('404), claims 4-6 of copending Application No. 11/231494 ('494), and claims 20-41 of copending Application No. 11/495015 ('015).

Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1-8, 11, 15-22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 38, 39, 41-47, 49-51, 53-57, 60-65, 67, 68 and 97-101 of the instant application encompass a method for modulating an immune response comprising administering an inhibitor of Notch intracellular domain (Notch IC) protease activity in vivo wherein the inhibitor is a small molecule compound and down-regulates the Notch signaling pathway and a method of modulating the immune response to treat a T-cell mediated disease by the inhibitor. Claims 1-6, 8, 10, 12, 14-16 of '727 encompass a method for modifying cytokine expression in a cell comprising administering an inhibitor of Notch signaling pathway. Claims 16-32, 61-70, 72 of '989 encompass a method treating cancer and promoting an immune response by administering an inhibitor of Notch signaling. Claims 28-61, 86, 100-119 of '834 encompass a method for stimulating/increasing an immune response comprising administering an inhibitor of Notch signaling. Claims 1-16 of '422 encompass a method for modifying chemokine signaling in a cell comprising administering an inhibitor/modulator of the Notch signaling pathway. Claims 24-33 of '784 encompass a method for modulating Notch signaling in an immune cell or treating

an immune/inflammatory disorder comprising administering an inhibitor/modulator of the Notch signaling pathway. Claims 17-20 of '066 encompass a method for modulating the immune system in a mammal comprising administering a modulator of the Notch signaling pathway. Claims 1-20 of '724 encompass a method for modifying IL-4 expressing in a cell with a modulator of the Notch signaling pathway. Claims 1-7 of '796 encompass a method of treating graft versus host disease in a subject comprising administering a modulator of the Notch signaling pathway. Claims 65, 68-73 of '404 encompass a method for modulating an immune response comprising administering an inhibitor of Notch intracellular domain (Notch IC) protease activity in vivo wherein the inhibitor is a small molecule compound and down-regulates the Notch signaling pathway. Claims 4-6 of '494 encompass a method for modulating an immune response to an antigen in a subject by administering a particle comprising a polynucleotide coding for a modulator of the Notch signaling pathway. Claims 20-41 of '015 encompass a method for treating a disease or modulating an immune response by modulating the Notch signaling pathway by RNA interference agent.

Claims 1-8, 11, 15-22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 38, 39, 41-47, 49-51, 53-57, 60-65, 67, 68 and 97-101 of the instant application are unpatentable over claims 1-6, 8, 10, 12, 14-16 of '727, claims 16-32, 61-70, 72 of '989, claims 28-61, 86, 100-119 of '834, claims 1-16 of '422, claims 24-33 of 784, claims 17-20 of '066, claims 1-20 of '724, claims 1-7 of '796, claims 65, 68-73 of '404, claims 4-6 of '494, claims 20-41 of '015 because the claims of the copending applications and the instant application encompass an invention overlapping in scope. While language is not identical, the

inhibitors/modulators that inhibit/modulate an immune response as in copending application are also modulate the Notch signaling pathway since the activation of Notch signaling is regulated through the cleavage by presenilin to release the Notch IC, which overlaps the scope of the instantly claimed invention. Thus the instant and copending applications claim a non-distinct invention of the method of modulating an immune response by an inhibitor that down regulates the Notch IC protease activity regulated by presenilin or presenilin-dependent g-secretase

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

A search for inventors' names indicates that Applicant has filed several related applications. The rejections as set forth above only cover some of applications. It is incumbent on the applicant to inform the office of all related subject matter and to file all related terminal disclaimers. See 37 CFR 1.56, Duty to disclose information material to patentability.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-8, 11, 15-22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 38, 39, 41-47, 49-51, 53-57, 60-65, 67, 68 and 97-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6887475 (issued May 3, 2005, filed May 4, 1999, priority date Nov 6, 1997) and Hadland et al. (PNAS, 2001. June 19. 98: 7487-7491) in view of Strooper et al. (Nature. 1999. 398:518-5522 as in IDS).

US Patent No. 6887475 ('475) teaches that it may be therapeutically beneficial to modulate T cell function. '475 teaches that in conditions such as autoimmunity, allergy and graft rejection it is desirable to induce the downregulation of an immune response by stimulation of negative T cell or T cell-APC interaction to prevent an effective immunological attack. In other pathological conditions, such as tumor-induced immunosuppression, parasitic viral or bacterial infections, immunosuppression is a common feature and it would be desirable to inhibit the T cell interactions passing on the infectious tolerance as in claims 1-17, 38, 39, 67, 68 (see col.1 lines 18-36). '475 teaches that administration of Serrate/Delta prevents antigen priming of lymphocytes and normal T cell responses but induces regulatory T cell responses as in claims 27, 28, 30, 3, 33, 34 (see col.11-14, Examples 5-11). In addition, '475 teaches that Delta

induce immune tolerance (see Example 11). '475 teaches administration of Serrate/Delta reduces the production of IL-2 as in claims 42 (see col. Example 4). The teachings of '475 provide a motivation to one of skill in the art to enhance the cellular immunity that regulates tumor or infection by inhibiting the Notch signaling pathway by an inhibitor of the Notch signaling since activation of the Notch signaling pathway reduces T cell activation in allergy and immune tolerance and increases regulatory T cells. In addition, it is an inherent response that subsets of $CD4^+$ T cells and cytokines would be increased or decreased in response to an antigen or an inhibitor of the Notch signaling pathway in the immune system in vivo because activation of the Notch signaling pathway has effects on regulatory T cells and cytokines and are able to modulate maturation of $CD4^+$ or $CD8^+$ T cells. In addition the change of T cell activity and cytokines in an immune response as in claims 18-22, 24, 25, 27, 28, 30, 31, 33, 34, 42-47, 49-51, 53-57, 60-64 is evidenced by Hoyne et al. (Immunol. Rev. 2001. 182: 215-227, as in IDS). Thus, the responses of T cells and cytokines as well as the properties/features of different T cells and cytokines in response to an inhibitor of Notch IC protease activity as in claims 18-22, 24, 25, 27, 28, 30, 31, 33, 34, 42-47, 49-51, 53-57, 60-64 would be an inherent result of administration of the inhibitor. '475 fails to teach an agent modulating the Notch intracellular domain (Notch IC) protease activity and down regulating the Notch signaling pathway, wherein the Notch IC activity is regulated by presenilin or presenilin-dependent γ-secretase as recited in claims 1 and 97. '475 fails to teach MW167 as in claim 101.

Hadland et al. teach that Notch signaling is involved in maturation of $CD4^+CD8^+$ double positive thymocytes into $CD4^+$ or $CD8^+$ single positive T cells. Lowering the level of Notch IC by γ-secretase inhibitors inhibits the development of $CD8^+$ SP cells (see p. 7487, abstract. Hadland et al. PNAS, 2001. June 19. 98: 7487-7491). Lowering Notch1 activity after T cell receptor-directed lineage commitment represses the maturation of $CD8^+$ SP thymocytes but not $CD4^+$ SP cells. The teaching of Hadland et al. provides a motivation and a reasonable expectation of success in using γ-secretase inhibitors to modulate an immune response in vivo since γ-secretase inhibitors do affect maturation of specific subsets of T cells, which subsequently affect an immune response regulated by these T cells. Hadland et al. fail to teach MW167 as a γ-secretase inhibitor as recited in claim 101 and fail to teach the γ-secretase inhibitor is an inhibitor of Notch IC protease activity that is regulated by presenilin or presenilin-dependent g-secretase as recited in claim 1.

Strooper et al. teach that several γ-secretase inhibitors, including MW167, are able to inhibit the processing of Notch1 to release Notch IC (see p. 520, 1st col., 1st paragraph to 2nd col., 2nd paragraph). Strooper et al. teach that Notch signaling requires ligand-induced cleavage. The cleavage occurs within the transmembrane domain of Notch to release the intracellular domain of Notch. The process of Notch cleavage is similar to the process of γ-secretase mediated cleavage of APP, which is regulated by presenilin (p. 518, abstract). Presenilin deficiency reduces the proteolytic release of Notch IC as in claims 2, 3, 6, 7(p. 518, abstract). The teachings of Strooper et al. meet the limitation of an inhibitor of Notch IC protease activity and the limitations that the

protease is presenilin or presenilin-dependent γ-secretase as in claims 1-3, 6, 7 and MW167 as in claim 101.

It would have been obvious to one of ordinary skill in the art to be motivated to increase productive immunity against tumor or infection by inhibiting the Notch signaling since the activation of the Notch signaling pathway reduces T cell activation in immune tolerance. The person of ordinary skill in the art would have been motivated to use inhibitors of Notch IC protease activity in decreasing regulatory T cells and enhancing production of IL-5 in a condition such as tumor or infection to enhance a productive immunity instead of suppressing immunity, which is to pass tolerance to potentially enhance immune response of cytotoxicity $CD8^+$ and natural killer cells in cellular immunity. Thus, one of ordinary skill in the art would have expected success in downregulating regulatory T cells and IL-10 production by inhibiting the Notch signaling pathway by an inhibitor of the Notch IC protease activity since activation of Notch signaling reduces T-cell activation and increases regulatory T cells and IL-10 secretion. A down-regulation of regulatory T cells would decrease the production of IL-10. A γ-secretase inhibitor has been shown to have effects on inhibiting maturation of $CD8^+$ T cells but have no effect on $CD4^+$ T cell development, which would not affect the profiles of other cytokines regulated by normal $CD4^+$ T cells other than regulatory T cells. It would have been obvious for one of ordinary skill in the art at the time the instant invention was made to be motivated and have expected success in using an inhibitor of Notch IC protease activity, such as MW 167, to decrease regulatory T cells and IL-10 and increases the production of IL-5 in enhancing the immunity against tumor and

infection since activation of the Notch signaling pathway induces regulatory T cells and decreases IL-2 for a condition of immune tolerance and an γ-secretase inhibitor inhibiting the Notch signaling affects T cell development, which would subsequently affect the immune response.

Conclusion

NO CLAIM IS ALLOWED.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Hoyne et al. Immunology 2000. 100: 281-288.

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is

(571) 272-4521. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CYW
November 16, 2006

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